REMARKS

Upon entry of the present amendment, claims 10, 15, and 17-24 are canceled herewith in favor of new claims 25-34, which correspond roughly to the canceled claims as follows:

- New independent claim 25 replaces canceled claim 15;
- New dependent claims 26-31 and 33 replace canceled claims 17-24, respectively;
- New dependent claim 32 reflects a previously unclaimed preferred embodiment; and
- New dependent claim 34 replaces canceled claim 10.

All claims are directed to the invention of Group I elected in connection with the restriction requirement of November 13, 2007. Applicants respectfully submit that support for the claims as amended is found in the specification as originally filed; accordingly no new matter has been added. However, Applicants reiterate that this amendment is presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

In an effort to expedite prosecution, Applicants have canceled independent claim 15 and its dependents in favor of new claims 25 *et seq.* that more clearly specify that the composition at issue is a medicament for allergen-specific immunotherapy that:

- consists essentially of a purified recombinant polypeptide allergen derived from plant pollen bound to a three dimensionally cross-linked agarose bead by means of a covalent bond between the cross-linked agarose and a reactive group of said allergen; and
- is capable of inducing a strong allergen-specific IgG response comparable to that of an equivalent Alum-bound allergen with less granulomatous tissue reactions as compared to said Alum-bound allergen.

Applicants respectfully submit that the invention embodied by the pending claims is both adequately enabled and described in the specification as originally filed and thus request reconsideration and withdrawal of the outstanding grounds of rejection in view of the amendments, remarks, and evidence presented herewith.

Rejections Under 35 USC 112, First Paragraph

Claims 10, 15 and 17-24 stand finally rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement and written description requirements. While the Examiner finds the specification to adequately describe and enable a "microparticle consisting essentially of Phl p 5b covalently bound to CBP", she continues to find the following aspects to lack sufficient description and enabling support:

(a) medicaments for allergen-specific immunotherapy *capable of inducing strong antibody responses with less granulomatous tissue reactions*; and

(b) microparticles consisting essentially of beads of *any* three dimensionally cross-linked agarose and polypeptide allergens derived from *any* plant pollen, *any* grass pollen, *any* timothy grass pollen.

Applicants respectfully submit that cancellation of claims 10, 15 and 17-23 renders moot the outstanding rejections. Nevertheless, in the hopes of expediting prosecution and clarifying the issues at hand, Applicants offer the following comments:

Enablement:

The Examiner has repeatedly asserted that enablement of Applicants' invention is limited to the single working embodiment disclosed (i.e, the 2 μm cyanogen bromide activated spherical Sepharose CBP-rPhl p 5b particles of the examples). However, Applicants respectfully submit that the Examiner is holding Applicants to an unacceptably stringent standard that finds no basis in the law or fact. In particular, it well-settled that a specification is **presumed** to be enabled. Accordingly, the burden is on the Examiner to affirmatively demonstrate, through a showing of **compelling evidence**, that the claimed invention **could not** be performed without undue experimentation.

In this case, the Examiner's conclusion of non-enablement is rooted almost entirely in her own conjecture and speculation, including assertions of a generalized "unpredictability in the art" and doubt as to whether embodiments other that those disclosed would in fact operate as disclosed and possess the asserted beneficial utility. However, nothing in the record, when afforded its most reasonable interpretation, supports the Examiner's position that factors such as particle size, bead composition, allergen character and the like are so critical as to

undermine enablement of the invention of the presently claimed medicaments – which, in an effort to expedite prosecution, Applicants have voluntarily limited to **microparticles** (a term generally accepted in the art as referring to particles between 0.1 and 100 μm in diameter[1]) consisting essentially of three dimensionally cross-linked **agarose** beads covalently bound to purified recombinant polypeptide **plant pollen allergens**.

As for evidence of record, Applicants respectfully submit that the Examiner has fundamentally mischaracterized the Grönlund (Immunology, 2002) and Neimart-Andersson (Allergy, 2008) disclosures as supporting the criticality of the noted parameters. While Grönlund and Neimart-Anderdersson indeed hail the importance of "CBPs", they, like Applicants, use this abbreviation to refer generically to "**c**arbohydrate-**b**ased **p**articles" and not **c**yanogen **b**romide-activated spherical Sepharose **p**articles as the Examiner suggests. See lines 4-5 of the Gronlund (Immunology 2002) abstract, line 4 of the Neimart-Anderson abstract, and the bottom of page 3 of the instant specification. As for particle size, while Neimart-Anderson expressly "speculate" that particles on the order of 2 μm are "optimal for phagocytosis by antigen-presenting cells" and ingestion by monocyte derived dendritic cells, it is an error to characterize this as anything but discussion of a preferred embodiment, particularly in view of the subsequent reference to the findings of Kundig et al. (reference #31: J. Allergy Clinical Immunology, 2006, 117: 1470-1476), demonstrating the utility of virus-sized particles (i.e., particles on the order of 10 to 300 μm[2]). Thus, Applicants respectfully submit that there is no suggestion in the art that inventive particles outside the 2 μm range would **not** be suitable for ASIT. In any event, the data presented herewith confirm the utility of particles of varying size, in addition to varying substrate material and allergen type. See the data of Appendices A and B summarized in Appendix C and discussed in greater detail below.

In resolving her position on enablement, the Examiner summarily concludes that "*the specification does not adequately show, nor does the state of the art teach, that the genus of purified recombinant plant pollen polypeptide allergens coupled to any agarose bead may be used in a medicament for allergen-specific immunotherapy.*" (See May 29, 2009 Office Action at point 5, page 7). However, Applicants respectfully submit that evidence of actual unpredictability is lacking. Moreover, the evidence presented to date and herewith clearly

[1] See http://en.wikipedia.org/wiki/Microparticles
[2] See http://en.wikipedia.org/wiki/Virus

supports Applicants' position that:

(a) Recombinant allergens, like their respective natural counterparts, find ready utility in the context of allergen-specific immunotherapy (ASIT). See the references to D. Kraft et al. (*Int Arch Allergy Immunol*, 1999, vol. 118: 171-176 entitled "The Importance of Recombinant Allergens for Diagnosis and Therapy of IgE-Mediated Allergies") and R. Valenta et al. (*J Allergy Clin Immunol*, 2007, vol 119 (4): 826-830 entitled "Recombinant Allergens for Immunology") cited in the enclosed information disclosure statement; and

(b) One of skill in the art would reasonably expect the medicaments of the present invention to operate in a manner analogous to conventional Alum-adsorbed allergy vaccines, including an allergen-specific IgG response similar to that of Alum-based particles. To that end, Applicants again direct the Examiner's attention to the Vrtala reference referenced in the instant specification at pp. 8 and 9 (*J. Immunol.*, 2000, 165:6653-9, and 1998, 160:6137-40) as well as the Ball and Van Neuve publications, reference numbers 28 and 29 cited in the above-referenced Grönlund (Immunology, 2002) publication, which serves as the basis for the instant application.

Taken together, these facts suggest that the microparticles of the instant invention, like their alum adjuvant analogs, would find extensive utility and operability as allergen-specific immunotherapy (ASIT) medicaments.

Nevertheless, in an effort to convince the Examiner of the wide applicability of the instant invention, Applicants present herewith the sworn statement of Professor Rudolph Valenta, including data confirming the predicted efficacy of alternate embodiments of the instant invention. As a co-inventor of the present invention and a recognized expert in the art of allergen-specific immunotherapy (ASIT), Professor Valenta is well suited to assess what would be within the purview and expectation of one of ordinary skill. As noted in points 8 and 9 of the enclosed declaration, it is the informed opinion of Professor Valenta that "**c**arbohydrate-**b**ased **p**articles ('CBPs') may be readily and routinely substituted for conventional aluminium-hydroxide as a vaccine adjuvant useful in the context of allergen-specific immunotherapy (ASIT) with predictable and beneficial results" and that, given the positive findings of the experimentation to date, "one of ordinary skill would reasonably expect further combinations of the present invention to indeed be 'capable of inducing a

strong allergen-specific IgG response comparable to that of an equivalent Alum-bound allergen with less granulomatous tissue reactions as compared to said Alum-bound allergen'" as the instant claims require.

The significant supporting data of record and presented herewith is summarized in Appendix C. As noted therein, medicaments composed of microparticles of the present invention are capable of inducing pronounced allergen-specific IgG responses comparable to those of an Alum-based equivalent, but with reduced inflammatory reactions (including a reduced granulomatous response), regardless of particle size (e.g., mean diameter of 2.1 to 30 μm), substrate material (e.g., beaded agarose, cyanogen bromide activated agarose, N-hydroxysuccinimide actived agarose), and allergen type (timothy grass, cat dander, birch pollen). In fact, the data presented herein supports enablement of the invention **beyond** that of the pending claims (i.e., extending to recombinant peptides other than plant pollen allergens). Thus, it is the informed opinion of Professor Valenta and accordingly the position of Applicants that "given the high level of skill of the ordinary artisan, the ample direction and guidance provided by the instant disclosure, and the routine and conventional nature of the requisite comparative and confirmatory protocols . . . any experimentation needed to determine whether a particular combination indeed meets this criteria **cannot be fairly characterized as 'undue'** " (emphasis added).

In summary, Applicants respectfully submit that the *in vitro* and *in vivo* data presented in the instant specification and herewith demonstrate that a reasonable correlation exists between the scope of the claims and the scope of enablement. Accordingly, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the claims 25-35 without undue experimentation and with a reasonable expectation of success.

Written Description:

As with enablement, the Examiner has repeatedly asserted that description of Applicants' invention is essentially limited to the single working embodiment disclosed (i.e, the 2 μm cyanogen bromide activated spherical Sepharose CBP-rPhl p 5b particles of the examples). However, Applicants respectfully submit that the Examiner has misconstrued the requirements of the statute and is therefore holding Applicants to an unacceptably stringent standard that finds no basis in the law or fact.

As noted previously, it is well accepted that a specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without describing in detail **each and every** species within the genus described. In fact, even if the Examiner considers the subject matter of the claims to be broader than that disclosed in the original specification, the written description requirement may be satisfied if the broader concept would naturally occur to one skilled in the art upon reading the earlier specification.

In this case, the specification explicitly describes the invention's various components in terms of substrate material (see p. 2), microparticle size (see p. 2-3) and allergen type (see p. 3). Furthermore, Applicants clearly describe the disclosed invention as a universal alternative to traditional metal-based vaccine particles and therefore not restricted to a specific carbohydrate bead, polypeptide allergen, particle size or combination thereof. Thus, Applicants fail to see how the invention now claimed can be fairly characterized as beyond the bounds of the instant disclosure and the reasonable interpretation thereof.

As for the Examiner's conclusory statement that a "skilled artisan [could not] envision all the contemplated microparticle and medicament possibilities recited in the instant claims", Applicants respectfully submit that if one of skill in the art can readily envision all possible sequence variations falling within a range of percent identity (see Example 10 of the Written Description Training Materials, Revised March 25, 2008), then surely he can envision the various combinations of plant allergen and agarose particle encompassed by the present claims. As Professor Valenta notes in his sworn statement (see point 12), the presently claimed "genus" of ASIT medicaments, consisting essentially of agarose-plant pollen allergen microparticles, "lacks substantial variation and thus is adequately represented by the CBP-rPhl p 5b species described in the instant specification, with the rPhl p 5b polypeptide being sufficiently representative of the common attributes or features of the established class of 'recombinant polypeptide allergens derived from plant pollen' and cyanogen bromide-activated spherical Sepharose (also known as 'beaded agarose') being sufficiently representative of the common attributes or features of the established class of "three dimensionally cross-linked agarose beads.'" Thus, it is the informed opinion of Professor Valenta and further the position of Applicants "that the

originally filed application reasonably conveys to a person of ordinary skill in the art that Applicants were in possession of the presently claimed subject matter, including the limitations in question."

In summary, Applicants respectfully submit that when one weighs the extensive supporting evidence presented previously and herewith against the unsubstantiated speculation and conjecture of record, one must find in favor of Applicants and conclude that the presently claimed invention meets the requirements for enablement and written description set forth 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully petitions for withdrawal of all grounds of rejections in favor of the issuance of a timely notice of allowance.

CONCLUSION

The Petition for a One-Month Extension of Time extends the outstanding response deadline from **January 29, 2010** to on or before **March 1, 2009** (February 28th being a Sunday). Thus, Applicants respectfully submit that this response is timely and no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: **March 1, 2010**

By: **/chalin a. smith/**

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